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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/549,665

09/19/2005

Adrian Merlo

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10/20/2009

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EXAMINER

SCHLIENTZ, LEAH H

ART UNIT

PAPER NUMBER

1618

MAIL DATE

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10/20/2009

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/549,665	<b>Applicant(s)</b> MERLO ET AL.	
	<b>Examiner</b> Leah Schlientz	<b>Art Unit</b> 1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 22 June 2009.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-13 and 17-30 is/are pending in the application.
- 4a) Of the above claim(s) 1-13 and 21-28 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 17-20 and 29-30 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)          | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

## **DETAILED ACTION**

### ***Acknowledgement of Receipt***

Applicant's Response, filed 6/22/2009, in reply to the Office Action mailed 3/20/2009, is acknowledged and has been entered. Claims 1-13 and 17-30 are pending, of which claims 1-13 and 21-28 are withdrawn from consideration at this time as being drawn to a non-elected invention. Claims 29 and 30 have been amended. Claims 17-20 and 29-30 are readable upon the elected invention and are examined herein on the merits for patentability.

### ***Response to Arguments***

Any rejection not reiterated herein has been withdrawn as being overcome by amendment.

Applicant's arguments have been fully considered but are not persuasive for reasons set forth hereinbelow.

### ***Information Disclosure Statement***

The information disclosure statements submitted 1/13/2006, 7/18/2006 and 11/14/2007 were previously considered and initially by the examiner. Copies of the signed IDS sent with the previous Office Action mailed on 3/20/2009 are viewable in PAIR.

***Claim Rejections - 35 USC § 102***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 17-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Visser *et al.* (WO 92/18536), for reasons set forth in the previous Office Action.

Applicant argues on pages 21-23 of the Response that general formula I of Visser for labeled peptides amounts to several million different combinations, and that a person skilled in the art cannot find any hint in Visser *et al.* that would make him or her select the claimed compound among the millions of others disclosed therein: The examples of Visser *et al.* only describe conjugates comprising DTPA as the chelator moiety, and there is no disclosure in the description that would lead to the claimed compound. Applicant asserts that even if the generic formula (I) of Visser *et al.* in theory includes the above compound (together with several million others), it fails to particularly teach the species claimed in the present invention. In other words, the claimed species cannot be at once envisioned from the disclosure of Visser *et al.* as required for a finding of obviousness.

This is not found to be persuasive. A generic chemical formula can anticipate a claimed species covered by the formula when the species can be "at once envisaged" from the formula. See MPEP 2131.02. When the compound is not specifically named, but instead it is necessary to select portions of teachings within a reference and combine them, e.g., select various substituents from a list of alternatives given for placement at specific sites on a generic chemical formula to arrive at a specific

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composition, anticipation can only be found if the classes of substituents are sufficiently limited or well delineated. *Ex parte A*, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990). If one of ordinary skill in the art is able to "at once envisage" the specific compound within the generic chemical formula, the compound is anticipated. One of ordinary skill in the art must be able to draw the structural formula or write the name of each of the compounds included in the generic formula before any of the compounds can be "at once envisaged." One may look to the preferred embodiments to determine which compounds can be anticipated. *In re Petering*, 301 F.2d 676, 133 USPQ 275 (CCPA 1962). In the instant case, the sequence of substance p is well known in the art to be: Arg Pro Lys Pro Gln Gln Phe Phe Gly Leu Met. From the disclosure of Visser, one of ordinary skill would only need to select MetO<sub>2</sub> for Met from Visser's generic structure based on the known sequence of substance P to arrive at Applicant's claimed structure. Since the sequence of substance P is well known, one would immediately envisage making a selection of MetO<sub>2</sub> based on Visser's genus of three possible variations at this position (Met, MetO or MetO<sub>2</sub>). Or for example, one would immediately envisage making one of three selections for A<sub>7</sub> (e.g. Gly for Sar) for compound 2 of Visser. Likewise DOTA and DTPA are commonly exchangeable chelators in the diagnostic arts such that one would envisage substitution of one for the other, based upon Visser's disclosure that either chelator is suitable.

***Claim Rejections - 35 USC § 103***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 17-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Visser *et al.* (WO 92/18536) in view of Coy *et al.* (US 5,750,646), for reasons set forth in the previous Office Action.

Applicant argues on page 23 of the Response that Coy relates to linear peptide analogues, and mentions that natural amino acids, such as Thienylalanine (Thi), are interchangeable with Phe. Applicant asserts that however, since Visser *et al.* fails to teach all the other limitations of the present invention, combining the teachings of these references do not lead a person skilled in the art to the subject matter of claimed invention. Therefore, the subject-matter of the present invention is also inventive.

This is not found to be persuasive. Response to arguments pertaining to Visser are maintained as above.

***New Grounds for Rejection***

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

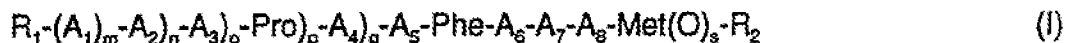
(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 17-20 and 29-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Visser *et al.* (WO 92/18536) in view of Li *et al.* (*Bioconjugate Chem.*, 2002, 13(4), p. 721-8).

Visser discloses methods for detecting and localizing tissues having neurokinine 1 receptors in the body of a warm-blooded living being by administration of a labeled small peptide having selective affinity to neurokinine 1 receptor, and by then radioassaying said being. The method also relates to therapeutic treatment of tumors (abstract). Diagnosis and therapy of gliomas are disclosed (page 1, lines 29+). A peptide having an affinity for neurokinine 1 receptors is labeled with (a) a detectable metal isotope selected from the group consisting of In-111, etc., said metal isotope being attached to said peptide via a suitable linker capable of reacting with an amino group, preferably a terminal amino group of said peptide, and having a chelating group for chelating said metal isotope (page 2, lines 19-28). The labeled peptide is derived from the following formula (page 4), including substance p and derivatives thereof in examples 1-5:



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wherein all of the symbols m, n, o, p and q are 1, or all but one of the symbols m, n, o, p and q are 1 and the remaining symbol is 0;

$R_1$  is a hydrogen atom or a  $C_1$ - $C_4$  alkylcarbonyl group;

$R_2$  is an amino group, a hydroxy group or a  $C_1$ - $C_4$  alkoxy group;

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$A_1$  is Arg, Gly or 5-oxo-Pro (pGlu);

$A_2$  is Pro or  $\beta$ -Ala;

$A_3$  is Lys or Asp;

$A_4$  is Gln, Asn or 5-oxo-Pro;

$A_5$  is Gln, Lys, Arg, N-acylated Arg or 5-oxo-Pro;

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or wherein  $A_5$  together with  $A_3$  forms a cystine moiety;

$A_6$  is Phe or Tyr;

$A_7$  is Gly, Sar or Pro;

$A_8$  is Leu or Pro; and

s is 0, 1 or 2;

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or a Tyr<sup>o</sup> derivative thereof.

See also compound 2, page 4. A suitable linker for attaching a metal isotope to the small peptide is provided with a chelating group, e.g. DOTA, etc (page 5, line 30- page 6, line 35). Pharmaceutical compositions including carrier, etc. are disclosed (page 7, lines 1-11). With regard to preparation of substance p analogue-chelator conjugates, Visser discloses solid-phase synthesis of peptide, and then reacting Lysine-protected substance p and DTPA-dianhydride. Labelling of DTPA-substance p is achieved by mixing with In-III chloride solution (page 10).

Visser does not disclose reaction of protected substance p analogue with DOTA(<sup>t</sup>Bu)<sub>3</sub>, as claimed. It is for this reason that Li is joined.

Li discloses attachment of DOTA to the D-Tyr<sup>1</sup> residue of somatostatin receptor D-TYR<sup>1</sup>-octreotate, allowing radiolabeling with radiohalogens and radiometals



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(abstract). Solid phase peptide synthesis was followed using Fmoc methodology.

DOTA-tris-(tert-butyl ester) was activated and coupled to Fmoc-protected amino acids (page 722, right column).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to substitute DOTA(<sup>t</sup>Bu)<sub>3</sub> as a functional equivalent reactant disclosed in the reaction coupling a chelator to peptide in Visser. The Supreme Court in KSR International Co. v. Teleflex Inc., 550 U.S. \_\_\_, 82 USPQ2d 1385, 1395-97 (2007) identified a number of rationales to support a conclusion of obviousness which are consistent with the proper “functional approach” to the determination of obviousness as laid down in Graham. One such rationale includes the simple substitution of one known element for another to obtain predictable results. The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. See MPEP 2143. In the instant case, the substituted components (DOTA/DTPA prochelators) and their functions were known in the art at the time of the instant invention. For example, Visser shows DTPA anhydride as a reactant for coupling chelator to peptide using Fmoc protected amino acids. Li shows DOTA(<sup>t</sup>Bu)<sub>3</sub> as a reactant for coupling chelator to peptide using Fmoc protected amino acids. One of ordinary skill in the art could have substituted one known reactant (prochelator) for another, and the results of the substitution would have been predictable, that is conjugation of a chelator to substance p analogue.

### ***Conclusion***

No claims are allowed at this time.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is (571)272-9928. The examiner can normally be reached on Monday - Friday 8 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/  
Supervisory Patent Examiner, Art Unit 1618

LHS